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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,202	12/04/2001	Keith D. Allen	R902/75658.234	6809

26619 7590 02/17/2006

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,202	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,16-21,23,24 and 29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,16-21,23,24 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The notice of appeal filed on 7/6/05 is defective because it was filed prematurely. Applicant must wait until the examiner considers the reply and the claims are rejected again before appealing from the Office action mailed in response to the reply by filing another notice of appeal under 37 CFR 41.31. The response sent 7-6-05 is being treated as a response to the non-final office action 4-2-05.

Claims 1-5, 7, 9-15, 25-28 have been canceled. Claims 6, 8, 16-24 and 29-35 remain pending and are under consideration in the instant office action.

Applicant's arguments filed 7-6-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The amendment filed 2-17-05 remains objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The addition of the application numbers into paragraph 3 of pg 10 is new matter. No support for the patent applications is found in the specification as originally filed. Deletion of application 08/971310 in paragraph 3 of pg 10 as teaching methods of preparing a targeting construct from a plasmid genomic library is also new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

The application number in pg 10, paragraph 4, must be updated upon being allowed.

Claim Rejections - 35 USC § 101

Claims 6, 8, 16-21, 23, 24 and 29-35 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for reasons of record.

Claims 6, 16-21, 23, 24 and 29-34 are directed toward a transgenic mouse whose genome comprises a null endogenous Kir5.1 allele.

Conquet (Neuropharmacology, 1995, Vol. 34, No. 8, pg 865-870) taught it was "obvious that this [gene knockout] technology does not give a definitive answer on the function of a gene, but the study of a mutant mouse helps to assess the contribution of this gene within a given process" (pg 868, col. 2, "Discussion", lines 6-10). The mice in the instant application do not give a definitive answer on the function of the Kir5.1 gene. Therefore, using the mice to reveal the function of the Kir5.1 gene is not a substantial utility because the mice may never reveal the function of the disrupted gene and because the "clues" obtained using the mice are not substantial enough to determine the function of the disrupted gene.

Using knockout mice for "further research" to determine gene function is not a substantial utility because knockout mice do not necessarily reveal the function of the knocked out gene. Bowery of record (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught

that despite administering antagonists to the mice, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-). Thus, knockout mice do not have a well-established utility for determining gene function because knockout mice do not necessarily reveal the function of the knocked out gene.

The phenotype of knockout mice may be a result of other genes compensating for the loss of the protein and not the disruption itself. Olsen of record (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

Thus, knockout mice may only provide clues to pathways, and knockout mice do not necessarily have phenotypes that reflect the function of the knocked out protein.

The art at the time of filing did not teach mice with a disruption in the Kir5.1 gene. However, the art at the time of filing taught mice with a disruption in GIRK2 (Kir3.2) are indistinguishable from wild-type mice, while *wv/wv* mice, having a single point mutation in the Kir3.2 gene, had extensive cerebellar granule cell death, dopaminergic neuronal loss in the substantia nigra, male infertility, and spontaneous seizures (Signorini, of record, 1997, PNAS, Vol. 94, pg 923-927). Thus, different mutations in inwardly rectifying potassium channels caused different phenotypes. The specification teaches making Kir5.1 -/- mice having dwarfed body shape (pg 53, lines 21-22), decreased body weight, spleen weight and spleen:body weight ratio (pg 54, lines 54), and increased startle response (pg 55, lines 8-11).

The specification suggests using the mice as a model of disease but does not disclose a specific disease in humans linked to a disruption in Kir5.1 (pg 18, lines 8-9; pg 19, lines 21-23). The specification suggests using the mice to compounds that alter a physiological response in the mice (pg 19, lines 5-20). The specification does not teach a disruption in Kir5.1 correlates to any specific disease or physiological response in humans, specifically increased startle response, dwarfism, decreased body weight, decreased spleen weight, or decreased spleen weight: body weight ratio as claimed. Using the mice claimed to identify compounds is not specific to the mouse claimed because wild-type mice may be used to identify such compounds. In fact, any mouse can be used to find compounds that modulate the startle response, size, body weight,

spleen weight, or spleen weight: body weight ratio. The specification teaches the "open field test" is generic to the hearing processing, sensory and motor processing, global sensory processing and motor abnormalities (pg 54, lines 20-25) as well as sensorimotor processing, attention, anxiety and thought disturbance (pg 54, lines 26-30); therefore, the "open field test" is not specific to any disease. Thus, using the mouse claimed to identify compounds is not specific to that mouse, and the mouse claimed does not have a use that is specific to any disease in humans.

Claim 16 requires the mice have increased startle response relative to a wild-type mouse. Claims 17 and 18 require the increased startle response is an indication of increased anxiety or a stimulus processing disorder.

Kir5.1 -/- mice had increased "prepulse inhibition" in an auditory "startle test" as compared to wild-type mice.

For a description of "prepulse inhibition" and the "startle test," read Bullock (Behavioral Neurosci. 1997. Vol. 111, pg 1353-1360) and Paylor (Psychopharmacology, 1997, Vol. 32, pg 169-180).

Bullock taught the startle responses of eight inbred mouse strains varied dramatically; therefore, Bullock concluded genetic factors contributed to regulating the startle response and the prepulse inhibition of the startle response. Bullock also determined the "prepulse inhibition" of acoustic startle did not correlate to "prepulse inhibition" of tactile startle; therefore, "acoustic startle" and "tactile startle" were regulated by different genetic factors. Bullock also concluded that genetic factors regulate some aspects of the startle response, but not others (pg 1358 "Discussion"

through pg 1389, line 5). The phenotype of decreased prepulse inhibition was a symptom known to be generic to schizophrenia, posttraumatic stress disorder, and obsessive-compulsive disorder in humans (pg 1353, ¶ bridging col. 1-2). Bullock, and the art at the time of filing as a whole, did not teach increased prepulse inhibition as claimed correlated to any symptom or any disease in humans.

Paylor also taught prepulse inhibition varied between mouse strains and that decreased prepulse inhibition was generic to a number of psychiatric disorders. Paylor noted "prepulse inhibition paradigm has quickly become the test of choice for scientists developing rodent models to study the mechanisms underlying the sensorimotor gating deficit observed in schizophrenia" (pg 169, col. 2, line20-24).

A mouse having increased startle response in a startle test or anxiety as claimed does not have a patentable utility because:

i) increased prepulse inhibition as claimed does not correlate to schizophrenia, posttraumatic stress disorder, obsessive-compulsive disorder, which have a decreased prepulse inhibition;

ii) abnormal prepulse inhibition is not specifically treated in humans. Therefore, using a mouse with abnormal prepulse inhibition to determine treatments for abnormal prepulse inhibition is not a substantial utility;

iii) Prepulse inhibition is a measure of disease and not a model of disease. Henry (Soc. For Neurosci. Abstracts. 1999, Vol. 25. No. 1-2. pp 449, #177.17) states, prepulse inhibition is a "multimodal phenomenon that provides an operational measure of sensorimotor gaiting, a process by which an organism screens or filters the large flow

of information from its surroundings". A process that is merely measured in a disease such as anxiety is not necessarily treated or representative of the disease. Since prepulse inhibition is multimodal, the patient having increased prepulse inhibition may not have a disruption in Kir3.3. Therefore, a mouse having a disruption in Kir3.3 and increased prepulse inhibition does not represent the multimodal nature of prepulse inhibition;

iv) Mice with abnormal prepulse inhibition are only used for further study. Brody (1004, Mol. Psychiatry, 2004, Vol. 9, pg 35-41; see abstract) states prepulse inhibition is "widely used to study the neurobiology of schizophrenia". Using mice with abnormal prepulse inhibition to determine mechanisms of actions of disease (to determine the cause of a disease) is not a substantial utility;

v) If one of skill wanted to find a drug that increased prepulse inhibition to treat schizophrenic patients, any mouse could be used, i.e. a wild-type mouse, a mouse with increased prepulse inhibition, or a mouse with decreased prepulse inhibition (see Grauer, Psycholpharm. 1999, Vol. 141, pg 405-412). Therefore, using the mouse claimed to find drugs that increase prepulse inhibition is not a specific utility because it is not specific to the mouse claimed;

vi) Likewise, if one of skill wanted to find a drug that decreased prepulse inhibition to treat patients with anxiety, any mouse could be used, i.e. a wild-type mouse, a mouse with increased prepulse inhibition, or a mouse with decreased prepulse inhibition. Therefore, using the mouse claimed to find drugs that decrease prepulse inhibition is not a specific utility because it is not specific to the mouse claimed;

and

vii) Harrison (2003, Mol. Cell. Neurosci., Vol. 24, pg 1170-1179) taught, "The underlying changes that occur in behavioural, genetic, or pharmacological models of PPI are poorly understood, not least because the associated circuitry is complex and is thought to include serial and parallel inputs from frontal areas into a pontine startle circuit". In other words, abnormal startle response may be caused by multiple gene disruptions in the startle circuit or by one disruption of any of a number of genes in the startle circuit. Therefore, using a mouse with a disruption in Kir5.1 asserted to be part of the "startle circuit" is not a substantial utility because it does not represent the entire "startle circuit" and does not represent other possible disruptions in the "startle circuit" that may have the same effect.

Therefore, Kir5.1 knockout mice with increased auditory startle response do not correlate to any disease in humans, are not models of disease and have a phenotype that is generic to the "startle circuit" and not the specific function of Kir5.1.

Claim 8, directed toward cells having a disrupted Kir5.1 gene, is included because the cells lack a specific and substantial utility for the reasons above.

Applicants repeat the argument that knockout mice had a "well-known utility," i.e. "for further study of these disorders and their association with the Kir5.1 gene." Applicants cite MPEP 2701 II(A)(3). Applicants' arguments are not persuasive for reasons of record and have been addressed above in the basis of the rejection. In particular, the MPEP states:

> An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. (underlining added)

The scientific "utility" known in the art does not rise to the level of "patentable utility" or a "well-established" utility. Using Kir5.1 knockout mice for "further research" as described in the art is not a well-established utility because the amount of "further research" required to determine the function of the Kir5.1 gene using the mice is significant and because the blaze marks to do so have not been set forth by applicants. The mice claimed do not have a "well-established utility" because such the "scientific utility" described in the art is not a substantial or specific utility.

In addition, the utility guidelines clearly state that further research is not a "substantial utility" (see underline portion above).

Applicants point to an NIH report from 2004, Austin (Nature Genetics, 2004, Vol. 36, No. 9, pg 921-924), The Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)), Gene VII (Lewin, Oxford University Press (2000)), Joyner (Gene Targeting: A Practical Approach, Oxford University Press, 2000), Matise (Production of targeted embryonic stem cell clones in Joyner) and Crawley (What's wrong with my mouse, Behavioral phenotyping of transgenic and knockout mice, Wiley-Liss, 2000) to establish the mice had "well-established" utility (pg 7-10 of response). Applicants' arguments are not persuasive.

First, the NIH report and Austin were not available until 2004 and cannot be used to establish what was "well-established" at the time of filing.

Second, while the NIH report suggests knockout mice may be models of disease, one mouse with lipoma or mice with increased pain sensitivity as claimed are not models of any disease because they are not symptoms of disease.

Lastly, the references merely suggest using knockout mice to study the function of targeted genes, which does not rise to the level of a substantial utility according to the utility guidelines. The NIH report states knockout mice can be used to elucidate gene function. Austin states null-reporter alleles should be created as a starting point for studying the function of every gene. The Molecular Biology of the Cell states mutant mice can be an invaluable tool for investigating gene function. Gene VII states knockout mice are used to investigate directly the importance and function of a gene. Joyner states gene targeting in ES is used to study gene function in a mammalian organism. Matise states knockout ES cells can be used to study gene function in cell culture and in vivo. Crawley states knockout mutations provide a means for understanding gene function. None of references teach the mice will determine the function of the gene. Applicants have used the mice in expression analysis and phenotype analysis tests, but applicants have not determined the function of the gene. Simply using the mice for further research of the Kir5.1 gene is not a specific or substantial utility. None of the references teach a specific or substantial utility for mice with a disruption in the Kir5.1 gene as claimed.

Applicants argue the data obtained from the mice has been subscribed to by at least three pharmaceutical companies; therefore, applicants conclude that those of skill would recognize the utility of the mice (¶ bridging pg 10-11). Applicants' argument is not persuasive. Sales may be evidence to overcome a 103 obviousness rejection, but there is no case law that establishes that "sales" are evidence of patentable utility. Evidence of sales is not evidence the mice have a "well-established" utility or a "specific utility" or a "credible utility."

Applicants argue the 103 contradicts the utility rejection (pg 11). Applicants' argument is not persuasive. The examiner has provided adequate reasoning to support both the 101 and 103 rejections. The desire of those of ordinary skill to gain clues as to the function of genes was well established at the time of filing. The fact that those of ordinary skill in the art desired to make knockout mice to gain clues as to the function of genes does not necessarily mean the mice would have a specific and substantial utility, i.e. that those of ordinary skill would determine the function of the gene from the clues provided by the mice. Evidence is provided by applicants who used the mice in various tests and gained clues regarding the gene but did not teach the function of the gene.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure for mice with the phenotype described (pg 13). Applicants cite Austin (cited above) and Doetschman (Lab. Animal Sci., 1999, Vol. 49, pg 137-143) who teach mice have much in common with humans and that knockouts will provide "information concerning gene function..." (pg 13-14 of response). Applicants' arguments are not persuasive. Not all claims are limited to mice with a

phenotype. Mice with increased startle response, dwarfism, decreased body weight, decreased spleen weight, or decreased spleen weight: body weight ratio do not correlate to any diseases. Mice that die while juveniles cannot be used to determine gene function because they are dead. The examiner has provided ample reasoning and evidence why those of skill in the art at the time of filing would doubt why each phenotype fails to have substantial utility. The examiner has provided ample reasoning why each asserted utility fails to have substantial and/or specific utility. Even applicants' own further research, i.e. the expression, physical and behavioral analysis did not reveal the function of the Kir5.1 gene. Significant further research in this case is required to use the mice with the phenotypes described to determine the function of the Kir5.1 gene. Therefore, using the mice with the phenotypes described to determine clues to the function of the Kir5.1 gene does not constitute a patentable utility.

Applicants are reminded that In re Schoenwald, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. In this case, the mouse claimed might only provide a clue to a developmental process or signal transduction pathway in which SEQ ID NO:1 is involved. This is not a specific utility because results from the tests may only indicate SEQ ID NO: 1 is involved in development or signal transduction pathway. The phenotype provides only a clue that SEQ ID NO: 1 is generically involved in development or a signal transduction pathway influenced by numerous proteins.

Applicants argue the mice can be used for "expression analysis" and cite Austin

again. Applicants' argument is not persuasive. The specification does not teach what promoter is driving the LacZ reporter gene; therefore, it cannot be determined how expression of LacZ is relevant to determining anything about SEQ ID NO: 1 (see Example 1). If LacZ is operably linked to the gene's promoter, the expression analysis revealed:

> "LacZ (beta-galactosidase) expression was detectable in brain, kidney and coagulating glands. LacZ expression was not detected in: spinal cord, sciatic nerve, eye, Harderian glands, thymus, spleen, lymph nodes, bone marrow, aorta, heart, lung, liver, gall bladder, pancreas, kidney, urinary bladder, trachea, larynx, esophagus, thyroid gland, pituitary gland, adrenal glands, salivary glands, tongue. skeletal muscle, skin, male and female reproductive systems." (pg 52, lines 18-23).

The expression analysis did not reveal the function of the Kir5.1 gene. The specification does not teach how to use the data obtained to determine the function of the gene. Therefore, using the mice claimed in expression analyses does not have substantial utility because the amount of "further research" to determine the function of Kir5.1 is at least immeasurable because the blaze marks for doing so have not been set forth by applicants. Applicants used the mice in "further research" studies in the Examples and did not determine the function of the gene; therefore, without evidence to the contrary, the mice claimed are not necessarily capable of determining the function of Kir5.1 as asserted by applicants.

Claim Rejections - 35 USC § 112

Claims 6, 8, 16-21, 23, 24 and 29-35 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific

or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for reasons of record.

Claims 6 and 29-34 are not enabled because the specification does not enable using a transgenic with a wild-type phenotype as encompassed by the claims. The transgenics of claims 6 and 29-34 do not recite any phenotype and encompass mice having a wild-type phenotype. The specification does not provide any use for a transgenic having a disruption in a Kir5.1 gene and a wild-type phenotype. The specification does not teach how to use mice whose genomes comprise an exogenous marker gene to determine the function of Kir5.1. Nor did the art at the time of filing. Without such guidance, it would require one of skill in the art undue experimentation to determine the function of Kir5.1 by expression analysis of the marker genes in the mouse.

Increased startle response in Kir5.1 knockout mice as described in the specification does not correlate to any "startle response" in claim 16 or any "stimulus processing disorder" in claim 17 because it does not represent visual startle response or other stimulus processing disorders such as deafness or dyslexia. Therefore, the phenotypes of "increased startle response" and "stimulus processing disorder" are not enabled for their full breadth.

Applicants' arguments have been considered but do not address the basis of the rejection. Applicants have not provided any evidence that the phenotype is inherent to all mice having any disruption in the Kir5.1 gene as broadly claimed. Nor have

applicants addressed how the auditory startle response correlates to any startle response as broadly claimed.

New Matter

Claims 6, 8, 16-21, 23, 24 and 29-35 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "null endogenous Kir5.1 allele" in claim 6 remains new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed. The phrases "null allele" and "Kir5.1 allele" cannot be found and raise indefinite rejections (see 112/2nd below).

A "null endogenous Kir5.1 allele" in claim 6 is new matter. Support has not been provided for the amendment and none can be found in the specification as originally filed. The specification does not distinguish endogenous and exogenous Kir5.1 alleles.

The phrase "increased startle response is an indication of increased level of anxiety" is new matter in claim 17. Support cannot be found in the specification on pg 55, lines 8-11, Figures or claims as originally filed. Pg 55, lines 8-11, is limited to auditory startle. The scope claimed is broader than that originally contemplated and is, therefore, new matter.

The phrase "tissue" in claim 8 is new matter. Support cannot be found in the specification, Figures or claims as originally filed.

The breadth of "selectable marker" in claim 31 is new matter. Support cannot be found in the specification, Figures or claims as originally filed.

Indefiniteness

Claim 6, 8, 16-21, 23, 24 and 29-35 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of a "Kir5.1 allele" in claim 6 remain indefinite. The specification defines Kir5.1 as "a sequence comprising SEQ m NO:1 or comprising the Kir5.1 sequence identified in GenBank as Accession No.: AB016197; GI: 3953532, or orthologs or homologs thereof." (pg 7, lines 1-4). However, it cannot be determined how much homology is required for a sequence to still be considered an "orthologue" or "homolog" thereof and still be a Kir5.1 allele.

Applicants' arguments do not address this rejection or the confusing definition provided in the specification.

The metes and bounds of a "null Kir5.1 allele" in claim 6 are indefinite. It is unclear if the phrase is limited to a mouse without any of the Kir5.1 gene, or if the phrase encompasses a mouse without any of the coding region of the Kir5.1 gene, a mouse with a disruption in the Kir5.1 gene, wherein said disruption does not allow production of functional Kir5.1, or a mouse with a disruption in the Kir5.1 gene, wherein said disruption causes less than normal amounts of functional Kir5.1. The metes and bounds of what applicants consider a "null" allele cannot be determined.

Applicants argue the phrase was known in the art; therefore, the phrase was

clear. Applicants' argument is not persuasive because the art taught numerous definitions of a null allele. The specification does not teach which definition to use.

The phrase "wherein the increased startle response is an indication of increased level of anxiety" in claim 17 is indefinite. The phrase implies the knockout mice have more anxiety than wild-type mice; however, wild-type mice do not have anxiety. The increased startle response may indicate anxiety in the knockout mice, but does not indicate increased anxiety as compared to wild-type mice. Applicants' arguments are noted but do not address the line drawn to determine when increased auditory startle response indicates the mouse has a stimulus processing disorder.

The metes and bounds of when a mouse has dwarfism in claims 19 and 20 remain unclear. The term is not defined in the specification or the art at the time of filing as it relates to mice. Applicants' arguments are noted but do not address the line drawn to determine when smaller size indicates the mouse has dwarfism as claimed.

Claim 19 remains indefinite because the metes and bounds of what applicants consider "growth abnormality" cannot be determined. The term "abnormal" is subjective and is not defined in the specification. Applicants' arguments are noted but do not address the line drawn to determine when growth is passes into the realm of abnormal.

Claims 31 remains indefinite because it depends on claim 1, which has been canceled.

Claim Rejections - 35 USC § 102

Claims 6, 8, 16-18, 29-33 and 35 remain rejected under 35 U.S.C. 102(b) as being anticipated by Signorini of record (1997, PNAS, Vol. 94, pg 923-927).

Signorini taught making homozygous and heterozygous transgenic mice having a disruption in inward rectifier protein Kir3.2 (GIRK2/Kir3.2) (pg 924, col. 2 2nd ¶). The mice were predisposed to seizures (pg 925, ¶ bridging col. 1-2), which is an indication of a "stimulus processing disorder" as claimed (18). The mice of Signorini inherently have increased startle response (16) because they have a predisposition to seizures, a "stimulus processing disorder." The mice of Signorini inherently have increased startle response that indicates anxiety (17) because they have a predisposition to seizures, a "stimulus processing disorder." The Kir3.2 is a Kir5.1 allele as claimed because it is an inward rectifier protein that shares homology with SEQ ID NO: 1, thus meeting applicants' definition in the specification of Kir5.1 genes. The construct used to make the mice had the exogenous neomycin resistance gene in the Kir3.2 gene (pg 924, Fig. 1C). The neo gene is a visible marker because it can be visualized by PCR. Any gene is capable of being expressed in the brain; therefore, the neo gene is capable of being expressed in the brain as claimed (33).

Applicants argue one of skill would understand the Kir5.1 allele as claimed refer to the mouse Kir5.1 allele that encodes SEQ ID NO: 1. Applicants' argument is not persuasive because the definition of Kir5.1 in the specification encompasses "homologs thereof." Applicants argue the GIRK2 gene is not a Kir5.1 gene. Applicants' argument is not persuasive because the GIRK2 is also known as Kir3.2. The Kir3.2 gene is a "Kir5.1 allele" as claimed because it is an inward rectifier protein that shares significant structural and functional homology with the gene encoding SEQ ID NO: 1, thus meeting applicants' definition in the specification of Kir5.1 genes.

Claim Rejections - 35 USC § 103

Claims 6, 8, 16-18, 29-33 and 35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Signorini (1997, PNAS, Vol. 94, pg 923-927) in view of Mouri (Genomics, 1998, Vol. 54, pg 181-182), both of record.

Signorini taught making homozygous and heterozygous transgenic mice having a disruption in inward rectifier protein Kir3.2 (GIRK2/Kir3.2) (pg 924, col. 2 2nd ¶). The mice were predisposed to seizures (pg 925, ¶ bridging col. 1-2), which is an indication of a "stimulus processing disorder" as claimed (18). The mice of Signorini inherently have increased startle response (16) because they have a predisposition to seizures, a "stimulus processing disorder." The mice of Signorini inherently have increased startle response that indicates anxiety (17) because they have a predisposition to seizures, a "stimulus processing disorder." The Kir3.2 is a Kir5.1 allele as claimed because it is an inward rectifier protein that shares homology with SEQ ID NO: 1, thus meeting applicants' definition in the specification of Kir5.1 genes. The construct used to make the mice had the exogenous neomycin resistance gene in the Kir3.2 gene (pg 924, Fig. 1C). The neo gene is a visible marker because it can be visualized by PCR. Any gene is capable of being expressed in the brain; therefore, the neo gene is capable of being expressed in the brain as claimed (33). Signorini did not teach disrupting SEQ ID NO: 1.

However, Mouri taught the nucleic acid sequence of the mouse Kir5.1 gene (GenBank Accession No: ABO16197; SEQ ID NO: 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in an inward rectifier protein as taught by Signorini wherein the inward rectifier protein was Kir5.1 as taught by Mouri. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the Kir5.1 gene instead of the Kir3.2 gene to gain clues as to the function of Kir5.1 in vivo. Signorini and others in the art support the motivational statement by exemplifying the desire of those skilled in the art to disrupt various inward rectifying proteins in mice to gain clues about their function in vivo.

Applicants' arguments have been considered but are not persuasive. Applicants have not pointed to one element that the combined teachings of Signorini and Mouri fail to teach. Applicants' argument that the combined references are not enabling is not persuasive because those of skill knew how to go from cDNA to making a knockout construct (references available).

Claims 6, 8, 16-18, 29-33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conquet (Neuropharm. 1995, Vol.34, No. 8, pg 865-870) in view of Mouri of record (Genomics, 1998, Vol. 54, pg 181-182) and supported by Signorini of record (1997, PNAS, Vol. 94, pg 923-927).

Conquet made a mouse with a heterozygous and homozygous disruption in a gene by inserting LacZ and neo genes into the gene (¶ bridging pg 865-866; pg 886, Fig. 1A; pg 868, Fig. 3 and col. 1, line 6-8 and 17-20). Conquet did not disrupt SEQ ID NO: 1.

However, Mouri submitted Database GenBANK Accession number AB016197 (SEQ ID NO: 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to disrupt a gene as taught by Conquet, wherein the gene was SEQ ID NO: 1 as taught by Mouri. One of ordinary skill in the art at the time the invention was made would have been motivated to specifically disrupt SEQ ID NO: 1 instead of the glutamate receptor gene described by Conquet to gain clues to the function of SEQ ID NO: 1 in vivo. Signorini supports the desire for those of ordinary skill in the art to disrupt any inward rectifying genes in knockout mice.

Applicants have not addressed this rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

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